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REGIONAL VARIATION IN PERCUTANEOUS PENETRATION OF ^{14}C CORTISOL IN MAN*

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Previously we reported hydrocortisone percutaneous penetration rates as estimated by amounts of radioactivity recovered in the urine under several experimental circumstances but always employing the ventral aspect of the human forearm (1). This study quantitates the effect of regional variation on percutaneous penetration of hydrocortisone.

METHOD

All subjects were normal male volunteers.

0.06 mg of hydrocortisone with 5 microcuries of 14C activity was dissolved in each 0.1 ml dose, using acetone as a solvent. The quantity of hydrocortisone applied is similar to the application of a 0.25 per cent topical preparation. A circular 13 sq cm area was delineated with petrolatum. The test material was applied with a micropipette and the acetone evaporated by gentle flowing. The subjects were requested not to wash the area for one day; the site was not protected. All urine was collected for 5 days and analyzed for ^{14}C by a method previously described (2). Results are expressed in per cent of the dose applied. Since about 75 per cent of an intravenous control-dose of hydrocortisone appears in urine in man, the actual penetration of the compound is somewhat larger than reported here (1).

RESULTS

Measurable absorption occurred through all regions except the heel.

Table I gives the mean values in each experiment for the total five day excretion and the rates of excretion in each collection period. We chose to compare absorption in each anatomic region with absorption through the ventral aspect of forearm (the area most commonly used and with which we have had the most experience). Variation between subjects was observed; the absorption ratios between anatomic sites in each subject showed a smaller variation. Subjects served as their own controls for the several areas examined.

Great differences were observed in absorption through various sites. Fig. 1 illustrates the ratio of the total excretion for each anatomic site to that of the ventral forearm. This varied from a trace for the heel (not illustrated) to a forty-two fold increase for the scrotum.

The figures demonstrate the excretion rates in each time period. The great differences in penetration required presenting this data in three graphs with different scales. Fig. 2 shows the excretion pattern for sites having an absorption less than that of the ventral aspect of the forearm: palm, ankle, foot. Fig. 3 shows this pattern for sites somewhat greater than that of the ventral aspect of the forearm: dorsal aspect of the forearm, back, axilla, scalp; Fig. 4 shows this pattern for sites showing a great increase over the ventral aspect of the forearm: forehead, angle of the jaw and scrotum.

The ^{14}C excretion rate was maximal in the second twelve hour period except for the foot and back. The maximum rate for the foot occurred during the third and fourth day. The highest rate for the back occurred in the second day. After the maximum, the excretion rates in general declined gradually, with measurable excretion in the fifth day.

DISCUSSION

Several generalizations can be made. Apparent absorption (estimated by amounts in the urine) is increased in areas where follicles are larger or more numerous (such as the forehead and scalp) and decreased where the stratum corneum is thicker (the foot). Our data suggest, but do not prove, that absorption takes place transepidermally and through hair follicles. The increased absorption in hairy areas may be due partly to structural differences in the stratum corneum, but the data suggest that much of the increase is due

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TABLE I

Effect of anatomic region on absorption of topical ^{14}C hydrocortisone (Urinary ^{14}C excretion expressed as % applied dose)

Anatomic region	No.	Excretion rate per 24-hours						Total excretion		
		Collection period (days)						Experiment	Forearm control	Ratio
		0–1/2	1/2–1	2	3	4	5			
Forearm (ventral)	6	.14	.32	.27	.23	.19	.12	1.04	1.04	1.0
Forearm (dorsal)	6	.15	.62	.34	.22	.14	.09	1.19	1.04	1.1
Foot arch (plantar)	3	.01	.03	.03	.04	.04	.03	0.17	1.27	0.14
Ankle (lateral)	3	.05	.14	.10	.05	.05	*	.31	.74*	0.42
Palm	6	.10	.29	.22	.14	.10	.06	.78	.94	0.83
Back	2	.10	.35	.40	.28	.25	.10	1.26	.72	1.7
Scalp	3	1.02	1.74	1.44	.82	.47	.29	4.41	1.23	3.5
Axilla	3	.62	1.28	.62	.66	.37	.28	3.07	.86	3.6
Forehead	3	1.78	5.09	3.13	.58	.31	.19	7.65	1.27	6.0
Jaw angle	6	4.50	7.84	3.72	1.28	.55	.29	12.25	.94	13
Scrotum	3	20.5	27.7	8.8	1.8	1.1	.2	36.2	.86	42

* Samples missing: control corrected to 4 day period.

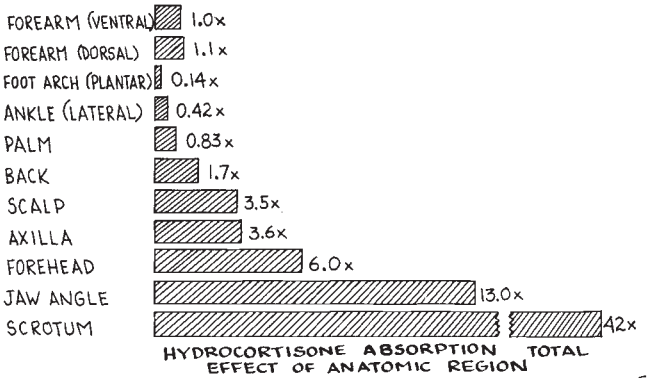

FIG. 1. Hydrocortisone absorption total-effect of anatomic region

to the presence of hair follicles, and probably occurs through them. In hairy areas, follicular absorption may be greater than transepidermal absorption.

These generalizations are not consistent with our observations of the palm and scrotum. Significant absorption occurred through the palm, which has a fairly thick stratum corneum and no hair follicles. The scrotum provides almost no barrier to hydrocortisone, quantitating the observation of Smith, Fischer and Blank (5). Other determining factors may be present in these regions of obvious specialization in structure and function.

Tragear (3) concluded that hair follicles do not increase skin penetration. His experiment compares disappearance of surface radioactivity of ^{32}P tributyl phosphate when applied around hair follicles and between hair follicles in the pig. His data show that tributyl phosphate is absorbed at a rate of 7 per cent per hour in hairless pig skin areas, while we find hydrocortisone is absorbed from hairless human skin areas at a rate of .02 per cent per hour. A compound absorbed this rapidly (300 times faster than hydrocortisone) may not show a prominent follicular component.

Others have noted penetration differences in different body areas. Cronin and Stoughton (4) have reviewed this data.

We previously observed clinically that psoriatic facial lesions respond more readily than body lesions. This may be related to the increased hydrocortisone absorption observed in the present study.

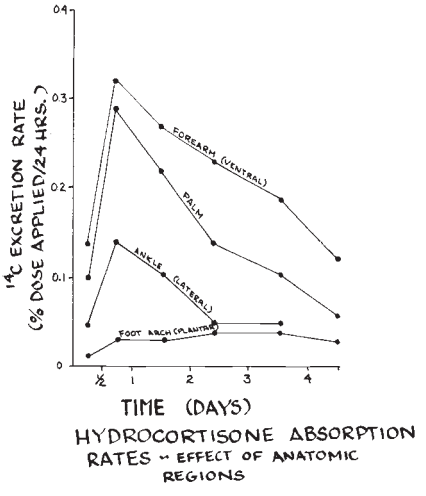

FIG. 2. Hydrocortisone absorption rates—effect of anatomic regions.

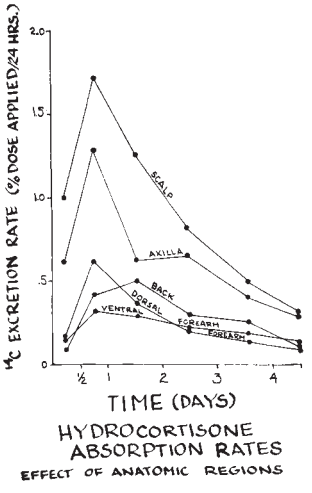

FIG. 3. Hydrocortisone absorption rates—effect of anatomic regions.

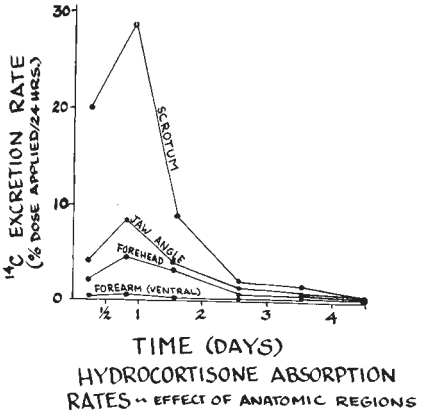

FIG. 4. Hydrocortisone absorption rates—effect of anatomic regions.

SUMMARY

1. Absorption of hydrocortisone occurs through all skin regions tested.

2. Absorption is increased in regions with large or numerous hair follicles. The scalp absorbed 3.5 times and the forehead 6 times the quantity of hydrocortisone as the ventral aspect of the forearm.

3. Absorption is decreased in some regions of skin having thickened stratum corneum, *e.g.* the foot.

4. In seeming contradiction, the palm is far from impenetrable to hydrocortisone.

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